Maintenance of Certification clinical management series

Series editor: James T. Li, MD, PhD

Use of omalizumab to improve desensitization safety in allergen immunotherapy

Désirée Larenas-Linnemann, MD, FAAAAI, Dist.Intl.FACAAI,[a] Ulrich Wahn, MD,[b] and Matthias Kopp, MD, PhD[c]

Mexico City, Mexico, and Berlin and Lübeck, Germany

INSTRUCTIONS

Credit can now be obtained, free for a limited time, by reading the review articles in this issue. Please note the instructions listed below:

1. Review the target audience, learning objectives and author disclosures.
2. Complete the pre-test online at www.jacionline.org (click on the Online CME heading).
3. Follow the online instructions to read the full version of the article, including the clinical vignette and review components.
4. Complete the post-test. At this time, you will have earned 1.00 *AMA PRA Category 1 CME Credit™*.
5. Approximately 4 weeks later you will receive an online assessment regarding your application of this article to your practice. Once you have completed this assessment, you will be eligible to receive 2 MOC Part II Self-Assessment credits from the American Board of Allergy and Immunology.

Date of Original Release: March 2014. Credit may be obtained for these courses until February 28, 2015.

Target Audience: Physicians and researchers within the field of allergic disease.

Accreditation/Provider Statements and Credit Designation: The American Academy of Allergy, Asthma & Immunology (AAAAI) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The AAAAI designates this journal-based CME activity for a maximum of 1 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

List of Design Committee Members: Désirée Larenas-Linnemann, MD, FAAAAI, Dist.Intl.FACAAI, Ulrich Wahn, MD, and Matthias Kopp, MD, PhD (authors), and James T. Li, MD, PhD (series editor)

Activity Objectives

1. Discuss whether omalizumab affects the immunomodulatory effects of immunotherapy.
2. Discuss in what kind of patient and to what degree omalizumab is able to reduce systemic adverse events caused by allergen subcutaneous immunotherapy (SCIT).
3. Discuss in what kind of patient and to what degree omalizumab is able to reduce systemic adverse events caused by venom immunotherapy.
4. Comment on the long-term effects of omalizumab that are only documented after prolonged use.

Recognition of Commercial Support: This CME activity has not received external commercial support.

Disclosure of Significant Relationships with Relevant Commercial Companies/Organizations: D. Larenas-Linnemann has consultant arrangements with MEDA, GlaxoSmithKline, Pfizer, Merck Sharp Dohme, and Novartis; has received research support from TEVA, Merck Sharp Dohme, Pfizer, GlaxoSmithKline, Novartis, Almirall, Senosiain, AstraZeneca, Sanofi, and MEDA; and has received payment for lectures from Pfizer, Merck Sharp Dohme, MEDA, GlaxoSmithKline, and AstraZeneca. M. Kopp is on the advisory boards for Novartis Pharma GmbH Germany and Meda Pharma GmbH & Co; has consultant arrangements with AbbVie Deutschland GmbH & Co, Allergopharma GmbH & Co. KG, and CHIESI GmbH; and has received payment for lectures from Novartis Pharma GmbH Germany, Nestlé Deutschland AG, GlaxoSmithKline, and Nutricia GmbH. U. Wahn declares that he has no relevant conflicts of interest. J. T. Li has consulted for Abbott.

CLINICAL VIGNETTE

The patient was a 34-year-old female nonsmoker with long-lasting allergic rhinitis, moderate persistent asthma during the winter months that was difficult to control without oral steroids, severe atopic dermatitis (AD), and a total IgE level of 293 IU/mL. She was started on sublingual immunotherapy (SLIT) with extracts of house dust mite, tree pollen, and cat (2 vials). Once attaining maintenance concentrations after a 1-month build-up, SLIT had to be interrupted because of a severe exacerbation of AD with punched-out erosions (eczema herpeticum) and uncontrolled asthma. After 6 months of omalizumab therapy, SLIT was restarted out of season without difficulty. She has been receiving SLIT maintenance therapy for half a year now, with very mild intermittent AD and only rescue asthma medication. The omalizumab dosing interval is slowly being increased from twice to once a month.

The full review of this article, including a preview of relevant issues to be considered, can be found online at www.jacionline.org. If you wish to receive CME or MOC credit for the article, please see the instructions above.

From [a]Hospital Médica Sur, Colonia Toriello Guerra, Delegación Tlalpan, Mexico City; [b]the Department for Pediatric Pneumology and Immunology, Charité University of Medicine, Berlin; and [c]the Department of Pediatric Allergy and Pulmonology, University Luebeck, Airway Research-Center North (ARCN), Member of the "Deutsches Zentrums für Lungenforschung" (DZL), Lübeck.

Received for publication October 22, 2013; revised December 11, 2013; accepted for publication December 17, 2013.

Corresponding author: Désirée Larenas-Linnemann, MD, FAAAAI, Dist.Intl.FACAAI, Hospital Médica Sur, Torre 2, cons. 602, Puente de Piedra 150, Colonia Toriello Guerra, Delegación Tlalpan, 14050 Mexico D.F., Mexico. E-mail: Marlar1@prodigy.net.mx.

0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2013.12.1089

REVIEW

Off-label use of omalizumab in combination with desensitization treatment has been studied for inhalant allergen subcutaneous immunotherapy (SCIT), subcutaneous venom immunotherapy (VIT), and oral food desensitization. The first omalizumab-SCIT combination trials sought to improve symptom reduction as opposed to that seen with SCIT alone. However, recent omalizumab desensitization trials have been focused on enhancing the safety of SCIT in high-risk patients.

Omalizumab after SCIT updosing to improve symptom reduction

The first trial was conducted by German investigators more than 10 years ago in 221 subjects who were 6 to 17 years old and had both birch pollen and grass pollen allergy. Half of the group was randomized to receive either birch pollen or grass pollen SCIT. After 14 weeks of SCIT updosing, each immunotherapy group was randomized to receive concomitant omalizumab or placebo over 24 weeks. Differences in symptom load were in favor of both omalizumab groups with statistical significance. This first trial concluded that additional clinical benefit of omalizumab was demonstrated in both pollen seasons, irrespective of whether patients were receiving SCIT.[E1,E2] Because omalizumab suppresses the IgE-mediated release of inflammatory mediators, researchers also questioned whether it would be possible to measure the anti-inflammatory effect of omalizumab by using the quantification of leukotriene release. Effectively, *in vitro* studies of patients' peripheral blood leukocytes showed a reduction in sulfidoleukotriene release in both SCIT plus omalizumab groups compared with that seen in the SCIT plus placebo groups.[E3] Also, SCIT combined with anti-IgE reduced nasal secretion tryptase and eosinophilic cationic protein levels.[E4] However, no difference in urinary leukotriene excretion could be detected between the SCIT plus omalizumab and SCIT plus placebo groups,[E5] and in a follow-up analysis 1 year after omalizumab, leukotriene release was no longer reduced in the postomalizumab group.[E6] Thus although omalizumab improved clinical scores in SCIT-treated patients, the effect of this 24-week treatment was not long-lasting, making the cost/benefit ratio questionable.

Preadministration and coadministration of omalizumab and SCIT updosing to improve safety

The design of several subsequent omalizumab-SCIT trials was the other way around because investigators planned to show whether omalizumab improves SCIT safety. One hundred fifty-nine adults with ragweed allergy were divided into 4 parallel groups; half of them received 9 weeks of premedication with omalizumab, and the other half received 9 weeks of premedication with placebo. Then each group was randomized to a 1-day rush updosing protocol of ragweed SCIT or placebo injections. Omalizumab reduced systemic reactions that required epinephrine from 15% to 2.6%.[E7] It was further shown that the combination of ragweed immunotherapy and anti-IgE resulted in prolonged inhibition of allergen-IgE binding (facilitated antibody analysis) compared with either treatment alone. The investigators concluded that these events might contribute to enhanced efficacy.[E8]

In another double-blind, placebo-controlled (DBPC) trial 248 allergic asthmatic patients whose symptoms were not controlled by inhaled corticosteroids underwent a build-up SCIT protocol after 16 weeks of premedication with placebo or omalizumab. The systemic reaction rate was reduced from 26.2% in the placebo plus SCIT group to 13.5% in the omalizumab plus SCIT group ($P = .017$), and more omalizumab-treated patients reached the maintenance dose (87.3% vs 72.1%, $P = .004$).[E9]

In 140 patients with seasonal allergic rhinitis and seasonal mild-to-moderate allergic asthma whose symptoms were not completely controlled with pharmacotherapy, omalizumab was added in a DBPC during the first 18 weeks of SCIT with a depigmented grass pollen–rye pollen extract (Depigoid; Laboratorios LETI Sl, Tres Cantos, Spain). During the core study, which encompassed the first pre-coseasonal period, there was a statistically significant difference in symptom severity in favor of the group treated with SCIT plus omalizumab (0.38 as opposed to 0.59, $P = .016$).[E10] However, during the 2-year extension of this DBPC trial in which all patients continued exclusively on SCIT, hardly any long-term effect of omalizumab could be found. Only lung function was slightly better in the group that received 4 months of omalizumab at the start of SCIT compared with the group that received only SCIT. As for the safety of starting SCIT under the umbrella of omalizumab during only the first months of SCIT, no problems with discontinuing omalizumab were reported. There were no severe adverse reactions reported in either group.[E11]

Premedication with omalizumab before subcutaneous VIT updosing to improve safety

Several case reports have been published on patients with (severe/near-fatal) anaphylaxis caused by Hymenoptera stings, who presented with a number of serious adverse reactions to VIT. In all cases the patients were able to tolerate with success the VIT once premedicated with 1 to 3 doses of 150 mg of omalizumab during a 1- to 6-week period. In 5 of the 7 cases, omalizumab was stopped after some months, and maintenance VIT treatment was continued without any problem. In the other 2 cases omalizumab was still an integral part of the combined therapy with VIT.[E12] However, in one VIT case omalizumab premedication over 6 months was not successful.[E13]

Long-term effect of omalizumab

In 18 asthmatic patients with cat or house dust mite allergy who had been receiving omalizumab for 6 years, asthma severity (determined based on questionnaire and lung function results), basophil allergen threshold sensitivity (CD sensitivity), and specific IgE and IgG_4 levels were examined after omalizumab withdrawal. Most of the patients had surprisingly mild asthma 12 to 14 months after omalizumab treatment, and several of them had reduced markers of allergic sensitization.[E14] Similar findings of the same patient group were still reported 3 years after omalizumab withdrawal.[E15]

In the quest for further long-term data on omalizumab, a retrospective analysis of total IgE levels in asthmatic patients treated over several years with omalizumab in 6 randomized DBPC trials and 1 epidemiologic study was conducted. The hypothesis that prolonged reduction of stimulation of the IgE receptor might lead to reduced IgE production was confirmed by Lowe and Renard.[E16] Searching for a mathematic feedback model in which long-term total IgE data would fit, it was shown that IgE production decreased by 54% per year on average.

However, as already discussed above, no long-term effect of the coadministration of omalizumab during the first months of SCIT was documented,[E11] possibly because of the reduced time span of omalizumab administration.

Some further safety issues

Safety data of the first DBPC trial of SCIT-omalizumab discussed above were published separately. There were 9 serious adverse reactions documented: 4 asthma exacerbations, all in the SCIT-only group; 2 headaches in the SCIT-omalizumab group; and 3 infections (2 in the SCIT plus verum group and 1 in the SCIT plus placebo group). Local side effects with SCIT were less in the omalizumab group.[E17]

During the premarketing phase of omalizumab, an imbalance had been registered between malignancies appearing in omalizumab recipients (0.5%) compared with control subjects (0.2%). However, recent in-depth analysis of 67 clinical trials with a total of 11,459 patients (7,789 treated with omalizumab) did not find any association of omalizumab treatment and risk of malignancy. In this large patient sample the rate ratio for malignancy in omalizumab-treated patients was less than for placebo-treated patients (0.93; 95% CI, 0.39-2.27), with no cluster of specific malignancy histologies identified either.[E18]

Omalizumab and oral food desensitization

A pilot study in 11 children with cow's milk allergy showed, for the first time, the benefit of pre-comedication with omalizumab from 9 weeks before and during a combined ultrarush 1-day partial updosing followed by a further 16-week more slow updosing phase. Even though all children experienced some adverse reactions, 9 of 11 children were able to tolerate a DBPC food challenge 8 weeks after stopping omalizumab and to continue a daily intake of 8000 mg of dairy products. One patient was able to take half of the normal daily dose, and there was 1 treatment failure.[E19]

Conclusion

The benefit of omalizumab in improving desensitization safety becomes most clear when accelerated protocols are used in highly sensitive patients. As such, omalizumab has shown clear benefit during SCIT (rush) updosing in patients with uncontrolled asthma and during VIT updosing in patients who presented with anaphylaxis during previous VIT updosing (1 patient with mastocytosis). Omalizumab also benefited subjects with severe cow's milk allergy in tolerating an oral desensitization protocol. In most patients omalizumab could be suspended without problems after several months of desensitization while the desensitization protocols are continued. On the other hand, in SCIT with regular extracts, slower updosing protocols, and more stable patients, the gain in safety with omalizumab is less clear because the several-month treatment of omalizumab in these patients was not enough to install any long-lasting effects.

THE CASE REVISITED

Thus in recent trials omalizumab has been shown to enhance the safety and tolerability of immunotherapy, especially SCIT and VIT. Because our patient experienced exacerbation of her cutaneous and respiratory allergy symptoms on attaining SLIT maintenance dosing, we proposed first pretreating her with omalizumab for some time and then restarting SLIT. Although shorter pretreatment with omalizumab might have been enough, our patient was not comfortable to restart SLIT after 6 months. Because short-term treatment with omalizumab does not seem to result in any long-term effects but, on the contrary, some data exist to suggest benefits after 6 years omalizumab, we have decided, for the time being, to continue both SLIT and omalizumab.

REFERENCES

E1. Kuehr J, Brauburger J, Zielen S, Schauer U, Kamin W, Von Berg A, et al. Efficacy of combination treatment with anti-IgE plus specific immunotherapy in polysensitized children and adolescents with seasonal allergic rhinitis. J Allergy Clin Immunol 2002;109:274-80.

E2. Rolinck-Werninghaus C, Hamelmann E, Keil T, Kulig M, Koetz K, Gerstner B, et al. The co-seasonal application of anti-IgE after preseasonal specific immunotherapy decreases ocular and nasal symptom scores and rescue medication use in grass pollen allergic children. Allergy 2004;59:973-9.

E3. Kopp MV, Brauburger J, Riedinger F, Beischer D, Ihorst G, Kamin W, et al. The effect of anti-IgE treatment on in vitro leukotriene release in children with seasonal allergic rhinitis. J Allergy Clin Immunol 2002;110:728-35.

E4. Bez C, Schubert R, Kopp M, Ersfeld Y, Rosewich M, Kuehr J, et al. Effect of anti-immunoglobulin E on nasal inflammation in patients with seasonal allergic rhinoconjunctivitis. Clin Exp Allergy 2004;34:1079-85.

E5. Kopp MV, Mayatepek E, Engels E, Brauburger J, Riedinger F, Ihorst G, et al. Urinary leukotriene E4 levels in children with allergic rhinitis treated with specific immunotherapy and anti-IgE (omalizumab). Pediatr Allergy Immunol 2003;14:401-4.

E6. Kopp MV, Stenglein S, Kamin W, Friedrichs F, von Berg A, Zielen S, et al. Omalizumab (Xolair) in children with seasonal allergic rhinitis: leukotriene release as a potential in vitro parameter to monitor therapeutic effects. Pediatr Allergy Immunol 2007;18:523-7.

E7. Casale TB, Busse WW, Kline JN, Ballas ZK, Moss MH, Townley RG, et al. Omalizumab pretreatment decreases acute reactions after rush immunotherapy for ragweed-induced seasonal allergic rhinitis. J Allergy Clin Immunol 2006; 117:134-40.

E8. Klunker S, Saggar LR, Seyfert-Margolis V, Asare AL, Casale TB, Durham SR, et al. Combination treatment with omalizumab and rush immunotherapy for ragweed-induced allergic rhinitis: inhibition of IgE-facilitated allergen binding. J Allergy Clin Immunol 2007;120:688-95.

E9. Massanari M, Nelson H, Casale T, Busse W, Kianifard F, Geba GP, et al. Effect of pretreatment with omalizumab on the tolerability of specific immunotherapy in allergic asthma. J Allergy Clin Immunol 2010;125:383-9.

E10. Kopp MV, Hamelmann E, Zielen S, Kamin W, Bergmann KC, Sieder C, et al. Combination of omalizumab and specific immunotherapy is superior to immunotherapy in patients with seasonal allergic rhinoconjunctivitis and co-morbid seasonal allergic asthma. Clin Exp Allergy 2009;39:271-9.

E11. Kopp MV, Hamelmann E, Bendiks M, Zielen S, Kamin W, Bergmann KC, et al. Transient impact of omalizumab in pollen allergic patients undergoing specific immunotherapy. Pediatr Allergy Immunol 2013;24:427-33.

E12. Galera C, Soohun N, Zankar N, Caimmi S, Gallen C, Demoly P. Severe anaphylaxis to bee venom immunotherapy: efficacy of pretreatment and concurrent treatment with omalizumab. J Invest Allergol Clin Immunol 2009;19:225-9.

E13. Soriano Gomis V, Gonzalez Delgado P, Niveiro Hernandez E. Failure of omalizumab treatment after recurrent systemic reactions to bee-venom immunotherapy. J Invest Allergol Clin Immunol 2008;18:225-6.

E14. Nopp A, Johansson SG, Ankerst J, Palmqvist M, Oman H. CD-sens and clinical changes during withdrawal of Xolair after 6 years of treatment. Allergy 2007;62: 1175-81.

E15. Nopp A, Johansson SG, Adedoyin J, Ankerst J, Palmqvist M, Oman H. After 6 years with Xolair; a 3-year withdrawal follow-up. Allergy 2010;65:56-60.

E16. Lowe PJ, Renard D. Omalizumab decreases IgE production in patients with allergic (IgE-mediated) asthma; PKPD analysis of a biomarker, total IgE. Br J Clin Pharmacol 2011;72:306-20.

E17. Kamin W, Kopp MV, Erdnuess F, Schauer U, Zielen S, Wahn U. Safety of anti-IgE treatment with omalizumab in children with seasonal allergic rhinitis undergoing specific immunotherapy simultaneously. Pediatr Allergy Immunol 2010;21:e160-5.

E18. Busse W, Buhl R, Fernandez Vidaurre C, Blogg M, Zhu J, Eisner MD, et al. Omalizumab and the risk of malignancy: results from a pooled analysis. J Allergy Clin Immunol 2012;129:983-9.e6.

E19. Nadeau KC, Schneider LC, Hoyte L, Borras I, Umetsu DT. Rapid oral desensitization in combination with omalizumab therapy in patients with cow's milk allergy. J Allergy Clin Immunol 2011;127:1622-4.